

**Claims**

1. A method for synthesising at least one molecule comprising the steps of
- 5 i) providing a plurality of connector polynucleotides each capable of hybridizing to at least 1 complementary connector polynucleotide,
- ii) providing a plurality of complementary connector polynucleotides selected from the group consisting of
- 10 a) complementary connector polynucleotides comprising at least 1 reactant, such as a functional entity comprising at least 1 reactive group,
- b) complementary connector polynucleotides comprising at least 1
- 15 reactive group,
- c) complementary connector polynucleotides comprising at least 1 spacer region,
- 20 iii) hybridizing at least 2 complementary connector polynucleotides to at least 2 connector polynucleotides,
- wherein at least 2 of said complementary connector polynucleotides
- 25 comprise at least 1 reactant, such as a functional entity comprising at least 1 reactive group,
- wherein at least 1 of said complementary connector polynucleotides hybridizes to at least 2 connector polynucleotides, and
- 30 iv) reacting at least 2 reactants or functional entity reactive groups by reacting at least 1 reactive group of each reactant or functional entity,
- wherein the reaction of said reactants or functional entity reactive groups
- 35 results in the formation of the molecule by reacting the reactive groups of the reactants provided by separate complementary connector

polynucleotides, or by covalently linking at least 2 functional entities provided by separate complementary connector polynucleotides.

- 5           2. The method of claim 1, wherein step iv) comprises reacting at least 3 reactants or functional entity reactive groups, such as at least 4 reactants or functional entity reactive groups, for example at least 5 reactants or functional entity reactive groups, such as at least 6 reactants or functional entity reactive groups, by reacting at least 1 reactive group of each reactant or functional entity.
- 10           3. The method of claim 1, wherein step iii) comprises
- iii) hybridizing at least 3 complementary connector polynucleotides to at least 2 connector polynucleotides,
- 15                 wherein at least 3 of said complementary connector polynucleotides comprise at least 1 reactant, such as a functional entity comprising at least 1 reactive group,
- wherein at least 1 of said complementary connector polynucleotides
- 20                 hybridizes to at least 2 connector polynucleotides,
- and wherein step iv) comprises
- iv) reacting at least 3 reactants or functional entity reactive groups by reacting at
- 25                 least 1 reactive group of each reactant or functional entity,
- wherein the reaction of said reactants or functional entity reactive groups results in the formation of the molecule by reacting the reactive groups of the reactants, or by covalently linking at least 3 functional entities provided by separate
- 30                 complementary connector polynucleotides.
4. The method of claim 3, wherein in step iv), at least 4 reactants or functional entity reactive groups are reacted, such as at least 5 reactants or functional entity reactive groups are reacted, for example at least 6 reactants or functional
- 35                 entity reactive groups are reacted, such as at least 8 reactants or functional

entity reactive groups are reacted, by reacting at least 1 reactive group of each reactant or functional entity.

5. The method of claim 1, wherein step iii) comprises

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iii) hybridizing at least 4 complementary connector polynucleotides to at least 2 connector polynucleotides,

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wherein at least 4 of said complementary connector polynucleotides comprise at least 1 reactant such as a functional entity comprising at least 1 reactive group,

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wherein at least 1 of said complementary connector polynucleotides hybridizes to at least 2 connector polynucleotides,

and wherein step iv) comprises

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iv) reacting at least 4 reactants or functional entity reactive groups by reacting at least 1 reactive group of each reactant or functional entity,

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wherein the reaction of said reactants or functional entity reactive groups results in the formation of the molecule by reacting the reactive groups of the reactants, or by covalently linking at least 4 functional entities provided by separate complementary connector polynucleotides.

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6. The method of claim 5, wherein in step iv), at least 5 reactants or functional entity reactive groups are reacted, such as at least 6 reactants or functional entity reactive groups are reacted, for example at least 8 reactants or functional entity reactive groups are reacted, such as at least 10 reactants or functional entity reactive groups are reacted, by reacting at least 1 reactive group of each reactant or functional entity.

7. The method of claim 1, wherein step iii) comprises

iii) hybridizing at least 5 complementary connector polynucleotides to at least 2 connector polynucleotides,

5 wherein at least 5 of said complementary connector polynucleotides comprise at least 1 reactants, such as a functional entity comprising at least 1 reactive group,

10 wherein at least 1 of said complementary connector polynucleotides hybridizes to at least 2 connector polynucleotides,

and wherein step iv) comprises

15 iv) reacting at least 5 reactants or functional entity reactive groups by reacting at least 1 reactive group of each reactant or functional entity,

20 wherein the reaction of said reactants or functional entity reactive groups results in the formation of the molecule by reacting the reactive groups of the reactants, or by covalently linking at least 5 functional entities provided by separate complementary connector polynucleotides.

25 8. The method of claim 7, wherein in step iv), at least 6 reactants or functional entity reactive groups are reacted, such as at least 7 reactants or functional entity reactive groups are reacted, for example at least 8 reactants or functional entity reactive groups are reacted, such as at least 10 reactants or functional entity reactive groups are reacted by reacting at least 1 reactive group of each reactant or functional entity.

30 9. The method of any of claims 1 to 8, wherein the molecule comprising reacted reactants or covalently linked functional entities is linked to the polynucleotide part of a complementary connector polynucleotide.

35 10. The method of any of claims 1 to 9 comprising the further step of cleaving at least one linker linking the molecule comprising reacted reactants or covalently linked functional entities to the polynucleotide part of a complementary connector polynucleotide.

11. The method of claim 10, wherein all linkers but 1 linker are cleaved, and wherein the linker not cleaved links the molecule to the polynucleotide part of a complementary connector polynucleotide.
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12. The method of any of claims 1 to 11, wherein complementary connector polynucleotides hybridized to connector polynucleotides are not linked by covalent bonds when reaction step iv) has been carried out, and/or wherein the polynucleotide part of different connector polynucleotides and/or different complementary connector polynucleotides are not covalently linked prior to the reactions of step iv).
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13. The method of claim 12 comprising the further step of linking the complementary connector polynucleotides, preferably by ligating the complementary connector polynucleotides, optionally preceded by initially performing a polynucleotide extension reaction resulting in individual complementary connector polynucleotides being linked together by covalent bonds.
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14. The method of any of claims 1 to 13, wherein connector polynucleotides hybridized to complementary connector polynucleotides are not linked by covalent bonds when reaction step iv) has been carried out, and/or wherein the polynucleotide part of different connector polynucleotides and/or different complementary connector polynucleotides are not covalently linked prior to the reactions of step iv).
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15. The method of claim 14 comprising the further step of linking the connector polynucleotides, preferably by ligating the connector polynucleotides, optionally preceded by performing a polynucleotide extension reaction resulting in individual connector polynucleotides being linked together by covalent bonds.
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16. The method of any of claims 1 to 11 comprising the further steps of
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- a) linking the complementary connector polynucleotides, preferably by ligating the complementary connector polynucleotides, optionally preceded by performing a polynucleotide extension reaction resulting in individual
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complementary connector polynucleotides being linked together by covalent bonds, and

- 5           b) linking the connector polynucleotides, preferably by ligating the connector polynucleotides, optionally preceded by performing a polynucleotide extension reaction resulting in individual connector polynucleotides being linked together by covalent bonds.

10       17. The method of any of claims 1 to 16, wherein the method does not involve ribosome mediated translation.

15       18. The method of any of claims 1 to 17 further comprising the step of hybridizing at least 1 further connector polynucleotide to at least 1 complementary connector polynucleotide, such as 2 or more complementary connector polynucleotides, hybridized to at least 1 connector polynucleotide, such as 2 or more connector polynucleotides, of the hybridisation complex of step iii).

20       19. The method of claim 18, wherein the further connector polynucleotide is selected from the group consisting of

- 25           a) connector polynucleotides comprising at least 1 functional entity comprising at least 1 reactive group,
- b) connector polynucleotides comprising at least 1 reactive group, and
- c) connector polynucleotides comprising at least 1 spacer region.

30       20. The method of any of claims 1 to 19 further comprising the step of hybridizing at least 1 further complementary connector polynucleotide selected from the group consisting of

- a) complementary connector polynucleotides comprising at least 1 functional entity comprising at least 1 reactive group,

b) complementary connector polynucleotides comprising at least 1 reactive group, and

c) complementary connector polynucleotides comprising at least 1 spacer region,

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to the hybridisation complex of step iii), such as to at least 1 connector polynucleotide, such as 2 connector polynucleotides, or to the at least 1 further connector polynucleotide hybridised in the method of claims 18 and 19, of said hybridisation complex, wherein said connector polynucleotide or further connector polynucleotide is preferably hybridized to at least 1 complementary connector polynucleotide, such as 2 or more complementary connector polynucleotides, for example 3 complementary connector polynucleotides, such as 4 complementary connector polynucleotides, for example 5 complementary connector polynucleotides, such as 6 complementary connector polynucleotides.

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21. The method of claim 18, wherein the step of hybridizing at least 1 further connector polynucleotide is repeated at least once, such as 2 times, for example 3 times, such as 4 times, for example 5 times, such as 6 times.

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22. The method of claim 20, wherein the step of hybridising at least one further complementary connector polynucleotide is repeated at least once, such as 2 times, for example 3 times, such as 4 times, for example 5 times, such as 6 times.

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23. The method of any of claims 1 to 22, wherein at least n connector polynucleotides and at least n-1 complementary connector polynucleotides are provided, n being an integer of from 3 to 6, and wherein each complementary connector polynucleotide hybridizes to at least 2 connector polynucleotides.

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24. The method of claim 23, wherein n is 3 or 4.

25. The method of any of claims 1 to 22, wherein at least n connector polynucleotides and at least n complementary connector polynucleotides are provided, n

being an integer of from 3 to 6, and wherein at least  $n-1$  complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.

5 26. The method of claim 25, wherein  $n$  complementary connector polynucleotides hybridize to at least 2 connector polynucleotides.

27. The method of any of claims 25 and 26, wherein  $n$  is 3 or 4.

10 28. The method of any of claims 1 to 22, wherein at least  $n$  connector polynucleotides and at least  $n+1$  complementary connector polynucleotides are provided,  $n$  being an integer of from 3 to 6, and wherein at least  $n-1$  complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.

15 29. The method of claim 28, wherein  $n$  complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.

30. The method of any of claims 28 and 29, wherein  $n$  is 3 or 4.

20 31. The method of any of claims 1 to 22, wherein at least  $n$  connector polynucleotides and at least  $n+2$  complementary connector polynucleotides are provided,  $n$  being an integer of from 3 to 6, and wherein at least  $n-1$  complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.

25 32. The method of claim 31, wherein  $n$  complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.

33. The method of any of claims 31 and 32, wherein  $n$  is 3 or 4.

30 34. The method of any of claims 1 to 22, wherein at least  $n$  connector polynucleotides and at least  $n+3$  complementary connector polynucleotides are provided,  $n$  being an integer of from 3 to 6, and wherein at least  $n-1$  complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.

35 35. The method of claim 34, wherein  $n$  complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.



36. The method of any of claims 34 and 35, wherein  $n$  is 3 or 4.
37. The method of any of claims 1 to 22, wherein at least  $n$  connector polynucleotides and at least  $n+4$  complementary connector polynucleotides are provided,  $n$  being an integer of from 3 to 6, and wherein at least  $n-1$  complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.
38. The method of claim 37, wherein  $n$  complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.
39. The method of any of claims 37 and 38, wherein  $n$  is 3 or 4.
40. The method of any of claims 1 to 22, wherein said plurality of connector polynucleotides comprises branched connector polynucleotides, wherein at least  $n$  branched connector polynucleotides and at least  $n$  complementary connector polynucleotides are provided,  $n$  being an integer of from 2 to 6, and wherein at least  $n-1$  complementary connector polynucleotide hybridize to at least 2 branched connector polynucleotides.
41. The method of claim 40, wherein at least  $n+1$  complementary connector polynucleotides are provided.
42. The method of any of claims 40 and 41, wherein at least  $n$  complementary connector polynucleotides hybridize to at least 2 branched connector polynucleotides.
43. The method of claim 42, wherein at least  $n+1$  complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.
44. The method of any of claims 40 to 43, wherein  $n$  is 3 or 4.
45. The method of claim 1 comprising the further step of repeating, for different connector polynucleotides and different complementary connector polynucleotides, the steps iii) and iv) at least once, such as 2 times, for example 3 times, such as

- 4 times, for example 5 times, such as 6 times, wherein the different complementary connector polynucleotides are hybridised, in each repeated step iii), to the hybridisation complex having been generated in the previous steps of the method, and wherein different functional entities are linked in each repeated step iv).
46. The method of any of claims 1 to 45, wherein a plurality of reactive groups of at least 1 functional entity of a complementary connector polynucleotide react with reactive groups of functional entities of at least 2 other complementary connector polynucleotides.
47. The method of claim 46, wherein the at least 1 functional entity comprises from 2 to 6 reactive groups.
48. The method of claim 47, wherein at least 3 of said reactive groups of said at least 1 functional entity react with at least 1 reactive group of at least 3 additional functional entities.
49. The method of any of claims 1 to 48, wherein said plurality of complementary connector polynucleotides comprise at least 2 complementary connector polynucleotides which are non-identical.
50. The method of any of claims 1 to 49, wherein said plurality of complementary connector polynucleotides comprise at least 2 branched complementary connector polynucleotides.
51. The method of any of claims 1 to 50, wherein said plurality of connector polynucleotides comprise connector polynucleotides comprising a sequence of n nucleotides, wherein n is an integer of from 8 to preferably less than 100, such as less than 80, for example less than 60, such as less than 40.
52. The method of claim 51, wherein said plurality of connector polynucleotides further comprise connector polynucleotides comprising at least 1 branching point connecting at least three polynucleotide fragments comprising a sequence of n

nucleotides, wherein n is an integer of from 8 to preferably less than 100, such as less than 80, for example less than 60, such as less than 40.

5 53. The method of any of claims 1 to 52, wherein said plurality of complementary connector polynucleotides comprise polynucleotides comprising a sequence of n nucleotides, wherein n is an integer of from 8 to preferably less than 60, such as less than 40, for example less than 20.

10 54. The method of claim 53, wherein said plurality of complementary connector polynucleotides further comprise polynucleotides comprising at least 1 branching point connecting at least three polynucleotide fragments comprising a sequence of n nucleotides, wherein n is an integer of from 8 to preferably less than 60, such as less than 40, for example less than 20.

15 55. The method of any of the preceding claims, wherein the polynucleotide part of at least one connector polynucleotide and/or at least one complementary connector polynucleotide is capable of undergoing self-hybridization.

20 56. The method of any of the preceding claims comprising the further step of covalently linking at least one connector polynucleotide to at least one complementary connector polynucleotide.

25 57. The method of any of the preceding claims, wherein the connector polynucleotides and/or the complementary connector polynucleotides are provided in batch.

30 58. The method of any of claims 1 to 56, wherein the connector polynucleotides and/or the complementary connector polynucleotides are provided sequentially, and wherein at least some functional entities provided with the connector polynucleotides and/or with the complementary connector polynucleotides are reacted before additional connector polynucleotides and/or the complementary connector polynucleotides are provided.

35 59. The method of claim 58, wherein reactive groups of functional entities are reacted when a) at least two connector polynucleotides comprising at least two

functional entities have been provided, and/or b) at least two complementary connector polynucleotides comprising at least two functional entities have been provided, and/or c) when at least one connector polynucleotide comprising at least one functional entity and at least one complementary connector polynucleotide comprising at least one functional entity have been provided.

60. A method for synthesising a plurality of different molecules, said method comprising

- i) providing a plurality of connector polynucleotides each capable of hybridizing to at least 1 complementary connector polynucleotide,
  - ii) providing a plurality of complementary connector polynucleotides selected from the group consisting of
    - a) complementary connector polynucleotides comprising at least 1 functional entity comprising at least 1 reactive group,
    - b) complementary connector polynucleotides comprising at least 1 reactive group,
    - c) complementary connector polynucleotides comprising at least 1 spacer region,
  - iii) hybridizing the plurality of connector polynucleotides and complementary connector polynucleotides, thereby forming a plurality of different hybridisation complexes, each hybridisation complex comprising at least 2 complementary connector polynucleotides and at least 2 connector polynucleotides,
- wherein, for each of said hybridisation complexes,
- at least 2 of said complementary connector polynucleotides comprise at least 1 functional entity comprising at least 1 reactive group, and

at least 1 of said complementary connector polynucleotides hybridizes to  
at least 2 connector polynucleotides, and

- iv) reacting at least 2 functional entity reactive groups of each complex by  
5 reacting at least 1 reactive group of each functional entity,

wherein, for each hybridisation complex, the reaction of said functional entity re-  
active groups results in the formation of a different molecule by covalently linking  
at least 2 functional entities provided by separate complementary connector  
10 polynucleotides, thereby synthesising a plurality of different molecules.

61. The method of claim 60, wherein different molecules are synthesised by the  
method of any of claims 1 to 59.
- 15 62. The method of any of claims 60 and 61 comprising the further step of selecting  
molecules having desirable characteristics, wherein the selection employs a  
predetermined assaying procedure.
- 20 63. The method of any of claims 60 to 62 comprising the further step of amplify-  
ing at least part of the individual connector polynucleotides used for the synthe-  
sis of a selected molecule, wherein optionally at least one PCR primer com-  
prises a functional entity and further optionally also part of the polynucleotide  
part of a connector polynucleotide.
- 25 64. The method of claim 63 comprising the further step of contacting a population of  
said amplified connector polynucleotides, or fragments thereof, with a plurality of  
complementary connector polynucleotides.
- 30 65. The method of claim 64 comprising the further step of performing an additional  
synthesis round by carrying out the steps of the method of any of claims 1 to 59  
using a population of said amplified connector polynucleotides or a population of  
said amplified connector polynucleotide fragments.
- 35 66. The method of any of claims 60 to 65 comprising the further steps of ligating, op-  
tionally preceded by a polynucleotide extension reaction, individual connector

polynucleotides, and ligating, optionally preceded by performing a polynucleotide extension reaction, individual complementary connector polynucleotides, wherein said ligation results in linking individual connector polynucleotides and/or individual complementary connector polynucleotides by covalent bonds.

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67. The method of claim 66 comprising the further steps of

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a) digesting said ligated connector polynucleotides and complementary connector polynucleotides,

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b) displacing the duplex polynucleotide strands generated by the ligation reaction, thereby generating single polynucleotide strands of ligated connector polynucleotides and ligated complementary connector polynucleotides, and

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c) contacting the single stranded polynucleotides generated in step b) with a plurality of complementary connector polynucleotides at least some of which comprises at least one functional entity comprising a reactive group.

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68. The method of claim 67 comprising the further step of performing an additional synthesis round by carrying out the steps of the method of any of claims 1 to 59 using as starting materials the population of connector polynucleotides obtained in step b) of claim 67, and the plurality of complementary connector polynucleotides provided in step c) of claim 67.

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69. The method of any of claims 60 and 61, wherein the plurality of complementary connector polynucleotides comprises from about 20 to about  $10^6$  different complementary polynucleotides, such as about 50 different complementary polynucleotides, for example about  $10^2$  different complementary polynucleotides, such as about  $10^3$  different complementary polynucleotides, for example about  $10^4$  different complementary polynucleotides, for example about  $10^5$  different complementary polynucleotides.

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70. The method of any of claims 60 and 61 comprising the further steps of

- a) linking individual connector polynucleotides by ligation and/or linking individual complementary connector polynucleotides by ligation,
- 5      b) synthesising a plurality of different molecules by reacting for each hybridization complex reactive groups of different functional entities, wherein each of said molecules are linked to a polynucleotide of the hybridization complex,
- 10      c) selecting and/or isolating desirable molecules linked to a polynucleotide of the hybridization complex by a predetermined selection procedure, including a binding assay,
- 15      d) isolating from selected and/or isolated hybridization complexes polynucleotides comprising individual connector polynucleotides linked by ligation, optionally amplifying said polynucleotides,
- 20      e) digesting said polynucleotides comprising individual connector polynucleotides and obtaining a plurality of connector polynucleotides, and
- 25      f) contacting the plurality of connector polynucleotides generated in step e) with a plurality of complementary connector polynucleotides at least some of which comprises at least one functional entity comprising a reactive group, and
- 30      g) performing a second or further round molecule synthesis using said plurality of connector polynucleotides and said plurality of complementary connector polynucleotides and employing the method of any of claims 1 to 59 for the synthesis of individual molecules.

30      71. The method of any of claims 60 and 61 comprising the further steps of

- a) linking individual connector polynucleotides by ligation and/or linking individual complementary connector polynucleotides by ligation,

- b) synthesising a plurality of different molecules by reacting for each hybridization complex reactive groups of different functional entities, wherein each of said molecules are linked to a polynucleotide of the hybridization complex,
- 5 c) selecting and/or isolating desirable molecules linked to a polynucleotide of the hybridization complex by a predetermined selection procedure, including a binding assay,
- 10 d) isolating from selected and/or isolated hybridization complexes polynucleotides comprising individual connector polynucleotides linked by ligation, optionally amplifying said polynucleotides,
- 15 e) contacting the plurality of polynucleotides comprising connector polynucleotides linked by ligation generated in step d) with a plurality of complementary connector polynucleotides each comprising at least one functional entity comprising a reactive group,
- 20 f) performing a second or further round molecule synthesis using said plurality of connector polynucleotides and said plurality of complementary connector polynucleotides and employing the method of any of claims 1 to 49 for the synthesis of individual molecules, and
- g) optionally repeating steps c) to f).
- 25 72. The method of any of claims 70 and 71, wherein steps a) and b) are performed sequentially in any order.
73. The method of any of claims 70 and 71, wherein steps a) and b) are performed simultaneously.
- 30 74. The method of any of claims 70 and 71, wherein steps a) and c) are performed sequentially in any order.
75. The method of any of claims 70 and 71, wherein steps a) and c) are performed simultaneously.
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## 76. The method of any of claims 60 to 75,

5 wherein the plurality of synthesised molecules are selected from the group consisting of  $\alpha$ -peptides,  $\beta$ -peptides,  $\gamma$ -peptides,  $\omega$ -peptides, mono-, di- and tri-substituted  $\alpha$ -peptides,  $\beta$ -peptides,  $\gamma$ -peptides,  $\omega$ -peptides, peptides wherein the amino acid residues are in the L-form or in the D-form, vinylogous polypeptides, glycopoly-peptides, polyamides, vinylogous sulfonamide peptides, polysulfonamides, conjugated peptides comprising e.g. prosthetic groups, polyesters, polysaccharides, polycarbamates, polycarbonates, polyureas, polypeptidylphosphonates, polyurethanes, azatides, oligo N-substituted glycines, polyethers, ethoxyformacetal oligomers, poly-thioethers, polyethylene glycols (PEG), polyethylenes, polydisulfides, polyarylene sulfides, polynucleotides, PNAs, LNAs, morpholinos, oligo pyrrolinones, polyoximes, polyimines, polyethyleneimines, polyimides, polyacetals, polyacetates, polystyrenes, polyvinyl, lipids, phospholipids, glycolipids, polycyclic compounds comprising e.g. aliphatic or aromatic cycles, including polyheterocyclic compounds, proteoglycans, and polysiloxanes, including any combination thereof,

20 wherein each molecule is synthesised by reacting a plurality of functional entities preferably in the range of from 2 to 200, for example from 2 to 100, such as from 2 to 80, for example from 2 to 60, such as from 2 to 40, for example from 2 to 30, such as from 2 to 20, for example from 2 to 15, such as from 2 to 10, such as from 2 to 8, for example from 2 to 6, such as from 2 to 4, for example 2, such as from 3 to 100, for example from 3 to 80, such as from 3 to 60, such as from 3 to 40, for example from 3 to 30, such as from 3 to 20, such as from 3 to 15, for example from 3 to 10, such as from 3 to 8, for example from 3 to 6, such as from 3 to 4, for example 3, such as from 4 to 100, for example from 4 to 80, such as from 4 to 60, such as from 4 to 40, for example from 4 to 30, such as from 4 to 20, such as from 4 to 15, for example from 4 to 10, such as from 4 to 8, such as from 4 to 6, for example 4, for example from 5 to 100, such as from 5 to 80, for example from 5 to 60, such as from 5 to 40, for example from 5 to 30, such as from 5 to 20, for example from 5 to 15, such as from 5 to 10, such as from 5 to 8, for example from 5 to 6, for example 5, such as from 6 to 100, for example from 6 to 80, such as from 6 to 60, such as from 6 to 40,

for example from 6 to 30, such as from 6 to 20, such as from 6 to 15, for example from 6 to 10, such as from 6 to 8, such as 6, for example from 7 to 100, such as from 7 to 80, for example from 7 to 60, such as from 7 to 40, for example from 7 to 30, such as from 7 to 20, for example from 7 to 15, such as from 7 to 10, such as from 7 to 8, for example 7, for example from 8 to 100, such as from 8 to 80, for example from 8 to 60, such as from 8 to 40, for example from 8 to 30, such as from 8 to 20, for example from 8 to 15, such as from 8 to 10, such as 8, for example 9, for example from 10 to 100, such as from 10 to 80, for example from 10 to 60, such as from 10 to 40, for example from 10 to 30, such as from 10 to 20, for example from 10 to 15, such as from 10 to 12, such as 10, for example from 12 to 100, such as from 12 to 80, for example from 12 to 60, such as from 12 to 40, for example from 12 to 30, such as from 12 to 20, for example from 12 to 15, such as from 14 to 100, such as from 14 to 80, for example from 14 to 60, such as from 14 to 40, for example from 14 to 30, such as from 14 to 20, for example from 14 to 16, such as from 16 to 100, such as from 16 to 80, for example from 16 to 60, such as from 16 to 40, for example from 16 to 30, such as from 16 to 20, such as from 18 to 100, such as from 18 to 80, for example from 18 to 60, such as from 18 to 40, for example from 18 to 30, such as from 18 to 20, for example from 20 to 100, such as from 20 to 80, for example from 20 to 60, such as from 20 to 40, for example from 20 to 30, such as from 20 to 25, for example from 22 to 100, such as from 22 to 80, for example from 22 to 60, such as from 22 to 40, for example from 22 to 30, such as from 22 to 25, for example from 25 to 100, such as from 25 to 80, for example from 25 to 60, such as from 25 to 40, for example from 25 to 30, such as from 30 to 100, for example from 30 to 80, such as from 30 to 60, for example from 30 to 40, such as from 30 to 35, for example from 35 to 100, such as from 35 to 80, for example from 35 to 60, such as from 35 to 40, for example from 40 to 100, such as from 40 to 80, for example from 40 to 60, such as from 40 to 50, for example from 40 to 45, such as from 45 to 100, for example from 45 to 80, such as from 45 to 60, for example from 45 to 50, such as from 50 to 100, for example from 50 to 80, such as from 50 to 60, for example from 50 to 55, such as from 60 to 100, for example from 60 to 80, such as from 60 to 70, for example from 70 to 100, such as from 70 to 90, for example from 70 to 80, such as from 80 to 100, for example from 80 to 90, such as from 90 to 100,

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wherein the functional entities of the above molecules can be linked by a chemical bond selected from the group of chemical bonds consisting of peptide bonds, sulfonamide bonds, ester bonds, saccharide bonds, carbamate bonds, carbonate bonds, urea bonds, phosphonate bonds, urethane bonds, azatide bonds, peptoid bonds, ether bonds, ethoxy bonds, thioether bonds, single carbon bonds, double carbon bonds, triple carbon bonds, disulfide bonds, sulfide bonds, phosphodiester bonds, oxime bonds, imine bonds, imide bonds, including any combination thereof,

or wherein the backbone structure of a synthesised molecule preferably comprises or essentially consists of one or more molecular group(s) selected from -NHN(R)CO-; -NHB(R)CO-; -NHC(RR')CO-; -NHC(=CHR)CO-; -NHC<sub>6</sub>H<sub>4</sub>CO-; -NHCH<sub>2</sub>CHRCO-; -NHCH<sub>2</sub>CH<sub>2</sub>CO-; -COCH<sub>2</sub>-; -COS-; -CONR-; -COO-; -CSNH-; -CH<sub>2</sub>NH-; -CH<sub>2</sub>CH<sub>2</sub>-; -CH<sub>2</sub>S-; -CH<sub>2</sub>SO-; -CH<sub>2</sub>SO<sub>2</sub>-; -CH(CH<sub>3</sub>)S-; -CH=CH-; -NHCO-; -NHCONH-; -CONHO-; -C(=CH<sub>2</sub>)CH<sub>2</sub>-; -PO<sub>2</sub><sup>-</sup>NH-; -PO<sub>2</sub><sup>-</sup>CH<sub>2</sub>-; -PO<sub>2</sub><sup>-</sup>CH<sub>2</sub>N<sup>+</sup>-; -SO<sub>2</sub>NH-; and lactams, including any combination thereof.

77. The method of any of claims 60 to 76, wherein said method results in the synthesis of more than or about 10<sup>3</sup> different molecules, such as more than or about 10<sup>4</sup> different molecules, for example more than or about 10<sup>5</sup> different molecules, such as more than or about 10<sup>6</sup> different molecules, for example more than or about 10<sup>7</sup> different molecules, such as more than or about 10<sup>8</sup> different molecules, for example more than or about 10<sup>9</sup> different molecules, such as more than or about 10<sup>10</sup> different molecules, for example more than or about 10<sup>11</sup> different molecules, such as more than or about 10<sup>12</sup> different molecules, for example more than or about 10<sup>13</sup> different molecules, such as more than or about 10<sup>14</sup> different molecules, for example more than or about 10<sup>15</sup> different molecules, such as more than or about 10<sup>16</sup> different molecules, for example more than or about 10<sup>17</sup> different molecules, such as more than or about 10<sup>18</sup> different molecules.

78. A method for identification of at least one molecule having desirable characteristics, said method comprising the steps of

- 5
- i) targeting a plurality of different molecules to a potential binding partner, wherein the plurality of different molecules are a) synthesised by the method of any of claims 60 and 61, or b) synthesised by the below mentioned method steps iii) and iv),
- 10
- ii) selecting at least one of said molecules having an affinity for said binding partner,
- 15
- iii) isolating connector polynucleotides from the selected molecules of step ii),
- 20
- iv) optionally, hybridizing the connector polynucleotides isolated in step iii) to a plurality of complementary connector polynucleotides selected from the group consisting of
- 25
- a) complementary connector polynucleotides comprising at least 1 functional entity comprising at least 1 reactive group,
- b) complementary connector polynucleotides comprising at least 1 reactive group,
- 30
- c) complementary connector polynucleotides comprising at least 1 spacer region,
- 35
- reacting the functional entity reactive groups, thereby generating at least one molecule by linking at least 2 functional entities provided by separate complementary connector polynucleotides, and
- performing steps i), ii), and iii) above for the at least one molecule generated in step iv), and
- v) decoding the nucleic acid sequence of isolated connector polynucleotides to reveal the identity of functional entities that have participated in the formation of the molecule(s) having an affinity for said binding partner.

- 5 79. A bifunctional molecule obtainable by the method of any of claims 1 to 59, said bifunctional molecule comprising a molecule part formed by reaction of functional entities, and a nucleic acid part formed by hybridisation between at least 2 complementary connector polynucleotide and at least 2 connector polynucleotides, wherein at least 2 of said polynucleotides comprise at least one functional entity comprising at least one reactive group the reaction of which results in the formation of the molecule part.
- 10 80. The bifunctional molecule according to claim 79 comprising at least n connector polynucleotides and at least n-1 complementary connector polynucleotides, n being an integer of from 3 to 6, wherein each complementary connector polynucleotide hybridizes to at least 2 connector polynucleotides.
- 15 81. The bifunctional molecule according to claim 79, wherein n is 3 or 4.
- 20 82. The bifunctional molecule according to claim 79 comprising at least n connector polynucleotides and at least n complementary connector polynucleotides, n being an integer of from 3 to 6, and wherein at least n-1 complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.
- 25 83. The bifunctional molecule according to claim 82, wherein n complementary connector polynucleotides hybridize to at least 2 connector polynucleotides.
- 30 84. The bifunctional molecule according to any of claims 82 and 83, wherein n is 3 or 4.
85. The bifunctional molecule according to claim 79 comprising at least n connector polynucleotides and at least n+1 complementary connector polynucleotides, n being an integer of from 3 to 6, and wherein at least n-1 complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.
86. The bifunctional molecule according to claim 75, wherein n complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.

87. The bifunctional molecule according to any of claims 75 and 76, wherein  $n$  is 3 or 4.
- 5 88. The bifunctional molecule according to claim 79 comprising at least  $n$  connector polynucleotides and at least  $n+2$  complementary connector polynucleotides,  $n$  being an integer of from 3 to 6, and wherein at least  $n-1$  complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.
- 10 89. The bifunctional molecule according to claim 88, wherein  $n$  complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.
90. The bifunctional molecule according to any of claims 88 and 89, wherein  $n$  is 3 or 4.
- 15 91. The bifunctional molecule according to claim 79 comprising at least  $n$  connector polynucleotides and at least  $n+3$  complementary connector polynucleotides,  $n$  being an integer of from 3 to 6, and wherein at least  $n-1$  complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.
- 20 92. The bifunctional molecule according to claim 91, wherein  $n$  complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.
93. The bifunctional molecule according to any of claims 91 and 92, wherein  $n$  is 3 or 4.
- 25 94. The bifunctional molecule according to claim 79 comprising at least  $n$  connector polynucleotides and at least  $n+4$  complementary connector polynucleotides,  $n$  being an integer of from 3 to 6, and wherein at least  $n-1$  complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.
- 30 95. The bifunctional molecule according to claim 79, wherein  $n$  complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.
- 35 96. The bifunctional molecule according to any of claims 94 and 95, wherein  $n$  is 3 or 4.

- 5 97. The bifunctional molecule according to claim 79, wherein said plurality of connector polynucleotides comprises branched connector polynucleotides, wherein at least n branched connector polynucleotides and at least n complementary connector polynucleotides are provided, n being an integer of from 2 to 6, and wherein at least n-1 complementary connector polynucleotide hybridize to at least 2 branched connector polynucleotides.
- 10 98. The bifunctional molecule according to claim 97 comprising at least n+1 complementary connector polynucleotides.
- 15 99. The bifunctional molecule according to any of claims 97 and 98, wherein at least n complementary connector polynucleotides hybridize to at least 2 branched connector polynucleotides.
100. The bifunctional molecule according to claim 99, wherein at least n+1 complementary connector polynucleotide hybridize to at least 2 connector polynucleotides.
- 20 101. The bifunctional molecule according to any of claims 97 to 100, wherein n is 3 or 4.
- 25 102. A composition or plurality of bifunctional molecules according to any of claims 79 to 101.
- 30 103. The composition or plurality according to claim 102 comprising at least about  $10^3$  different bifunctional molecules, such as more than or about  $10^4$  different bifunctional molecules, for example more than or about  $10^5$  different bifunctional molecules, such as more than or about  $10^6$  different bifunctional molecules, for example more than or about  $10^7$  different bifunctional molecules, such as more than or about  $10^8$  different bifunctional molecules, for example more than or about  $10^9$  different bifunctional molecules, such as more than or about  $10^{10}$  different bifunctional molecules, for example more than or about  $10^{11}$  different bifunctional molecules, such as more than or about  $10^{12}$  different bifunctional molecules, for example more than or about  $10^{13}$  different bifunctional
- 35

5 molecules, such as more than or about  $10^{14}$  different bifunctional molecules, for example more than or about  $10^{15}$  different bifunctional molecules, such as more than or about  $10^{16}$  different bifunctional molecules, for example more than or about  $10^{17}$  different bifunctional molecules, such as more than or about  $10^{18}$  different bifunctional molecules comprising different molecules.

- 10 104. The bifunctional molecule according to any of claims 79 to 101, or the plurality or composition comprising such bifunctional molecules according to any of claims 102 and 103,
- 15 wherein the said bifunctional molecules comprise molecules selected from the group consisting of  $\alpha$ -peptides,  $\beta$ -peptides,  $\gamma$ -peptides,  $\omega$ -peptides, mono-, di- and tri-substituted  $\alpha$ -peptides,  $\beta$ -peptides,  $\gamma$ -peptides,  $\omega$ -peptides, peptides wherein the amino acid residues are in the L-form or in the D-form, vinylogous polypeptides, glycopoly-peptides, polyamides, vinylogous sulfonamide peptides, polysulfonamides, conjugated peptides comprising e.g. prosthetic groups, polyesters, polysaccharides, polycarbamates, polycarbonates, polyureas, polypeptidylphosphonates, polyurethanes, azatides, oligo N-substituted glycines, polyethers, ethoxyformacetal oligomers, poly-thioethers, polyethylene glycols (PEG),
- 20 polyethylenes, polydisulfides, polyarylene sulfides, polynucleotides, PNAs, LNAs, morpholinos, oligo pyrrolinones, polyoximes, polyimines, polyethyleneimines, polyimides, polyacetals, polyacetates, polystyrenes, polyvinyl, lipids, phospholipids, glycolipids, polycyclic compounds comprising e.g. aliphatic or aromatic cycles, including polyheterocyclic compounds, proteoglycans, and polysiloxanes,
- 25 including any combination thereof,
- 30 wherein each molecule is synthesised by the method of any of claims 1 to 59 by reacting a plurality of functional entities preferably in the range of from 2 to 200, for example from 2 to 100, such as from 2 to 80, for example from 2 to 60, such as from 2 to 40, for example from 2 to 30, such as from 2 to 20, for example from 2 to 15, such as from 2 to 10, such as from 2 to 8, for example from 2 to 6, such as from 2 to 4, for example 2, such as from 3 to 100, for example from 3 to 80, such as from 3 to 60, such as from 3 to 40, for example from 3 to 30, such as from 3 to 20, such as from 3 to 15, for example from 3 to 15, such as from 3 to 10, such as from 3 to 8, for example from 3 to 6, such as from 3 to 4, for ex-
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ample 3, such as from 4 to 100, for example from 4 to 80, such as from 4 to 60,  
such as from 4 to 40, for example from 4 to 30, such as from 4 to 20, such as  
from 4 to 15, for example from 4 to 10, such as from 4 to 8, such as from 4 to 6,  
for example 4, for example from 5 to 100, such as from 5 to 80, for example from  
5 to 60, such as from 5 to 40, for example from 5 to 30, such as from 5 to 20, for  
example from 5 to 15, such as from 5 to 10, such as from 5 to 8, for example  
from 5 to 6, for example 5, such as from 6 to 100, for example from 6 to 80, such  
as from 6 to 60, such as from 6 to 40, for example from 6 to 30, such as from 6  
to 20, such as from 6 to 15, for example from 6 to 10, such as from 6 to 8, such  
as 6, for example from 7 to 100, such as from 7 to 80, for example from 7 to 60,  
such as from 7 to 40, for example from 7 to 30, such as from 7 to 20, for exam-  
ple from 7 to 15, such as from 7 to 10, such as from 7 to 8, for example 7, for  
example from 8 to 100, such as from 8 to 80, for example from 8 to 60, such as  
from 8 to 40, for example from 8 to 30, such as from 8 to 20, for example from 8  
to 15, such as from 8 to 10, such as 8, for example 9, for example from 10 to  
100, such as from 10 to 80, for example from 10 to 60, such as from 10 to 40, for  
example from 10 to 30, such as from 10 to 20, for example from 10 to 15, such  
as from 10 to 12, such as 10, for example from 12 to 100, such as from 12 to 80,  
for example from 12 to 60, such as from 12 to 40, for example from 12 to 30,  
such as from 12 to 20, for example from 12 to 15, such as from 14 to 100, such  
as from 14 to 80, for example from 14 to 60, such as from 14 to 40, for example  
from 14 to 30, such as from 14 to 20, for example from 14 to 16, such as from 16  
to 100, such as from 16 to 80, for example from 16 to 60, such as from 16 to 40,  
for example from 16 to 30, such as from 16 to 20, such as from 18 to 100, such  
as from 18 to 80, for example from 18 to 60, such as from 18 to 40, for example  
from 18 to 30, such as from 18 to 20, for example from 20 to 100, such as from  
20 to 80, for example from 20 to 60, such as from 20 to 40, for example from 20  
to 30, such as from 20 to 25, for example from 22 to 100, such as from 22 to 80,  
for example from 22 to 60, such as from 22 to 40, for example from 22 to 30,  
such as from 22 to 25, for example from 25 to 100, such as from 25 to 80, for  
example from 25 to 60, such as from 25 to 40, for example from 25 to 30, such  
as from 30 to 100, for example from 30 to 80, such as from 30 to 60, for example  
from 30 to 40, such as from 30 to 35, for example from 35 to 100, such as from  
35 to 80, for example from 35 to 60, such as from 35 to 40, for example from 40  
to 100, such as from 40 to 80, for example from 40 to 60, such as from 40 to 50,

for example from 40 to 45, such as from 45 to 100, for example from 45 to 80, such as from 45 to 60, for example from 45 to 50, such as from 50 to 100, for example from 50 to 80, such as from 50 to 60, for example from 50 to 55, such as from 60 to 100, for example from 60 to 80, such as from 60 to 70, for example from 70 to 100, such as from 70 to 90, for example from 70 to 80, such as from 80 to 100, for example from 80 to 90, such as from 90 to 100,

wherein preferably the functional entities of the above molecules can be linked by a chemical bond selected from the group of chemical bonds consisting of peptide bonds, sulfonamide bonds, ester bonds, saccharide bonds, carbamate bonds, carbonate bonds, urea bonds, phosphonate bonds, urethane bonds, azatide bonds, peptoid bonds, ether bonds, ethoxy bonds, thioether bonds, single carbon bonds, double carbon bonds, triple carbon bonds, disulfide bonds, sulfide bonds, phosphodiester bonds, oxime bonds, imine bonds, imide bonds, including any combination thereof,

or wherein preferably the backbone structure of a synthesised molecule preferably comprises or essentially consists of one or more molecular group(s) selected from -NHN(R)CO- ; -NHB(R)CO- ; -NHC(RR')CO- ; -NHC(=CHR)CO- ; -NHC<sub>6</sub>H<sub>4</sub>CO- ; -NHCH<sub>2</sub>CHRCO- ; -NHCHRCH<sub>2</sub>CO- ; -COCH<sub>2</sub>- ; -COS- ; -CONR- ; -COO- ; -CSNH- ; -CH<sub>2</sub>NH- ; -CH<sub>2</sub>CH<sub>2</sub>- ; -CH<sub>2</sub>S- ; -CH<sub>2</sub>SO- ; -CH<sub>2</sub>SO<sub>2</sub>- ; -CH(CH<sub>3</sub>)S- ; -CH=CH- ; -NHCO- ; -NHCONH- ; -CONHO- ; -C(=CH<sub>2</sub>)CH<sub>2</sub>- ; -PO<sub>2</sub><sup>-</sup>NH- ; -PO<sub>2</sub><sup>-</sup>CH<sub>2</sub>- ; -PO<sub>2</sub><sup>-</sup>CH<sub>2</sub>N<sup>+</sup>- ; -SO<sub>2</sub>NH<sup>-</sup> ; and lactams, including any combination thereof.

105. A method for selecting at least one bifunctional molecule from the composition of bifunctional molecules according to any of claims 102 to 104, said method comprising the steps of

- a) targeting a plurality of bifunctional molecules to a potential binding partner, and
- b) selecting or identifying at least one of said bifunctional molecules having an affinity for said binding partner.

106. The method of claim 105, wherein the identification of the bifunctional molecule comprises the steps of decoding the nucleic acid sequence of isolated connector polynucleotides to reveal the identity of functional entities that have participated in the formation of the molecule(s) having an affinity for said binding partner.
107. A method for evolving a plurality of bifunctional molecules according to any of claims 79 to 101, said method comprising the steps of
- a) selecting at least one bifunctional molecule,
  - b) isolating connector polynucleotides, or fragments of such polynucleotides, from said bifunctional molecule,
  - c) providing a plurality of complementary connector polynucleotides,
  - d) hybridising said isolated connector polynucleotides and said plurality of complementary connector polynucleotides,
  - e) reacting functional entity reactive groups of said complementary connector polynucleotides,
  - f) optionally repeating any combination of the aforementioned steps, and
  - g) evolving a plurality of bifunctional molecules each comprising a different molecule comprising covalently linked functional entities.
108. A method for synthesising at least one molecule, said method comprising the steps of
- i) providing a plurality of building block polynucleotides each capable of hybridizing to at least 1 other building block polynucleotide,
- wherein said building block polynucleotides are selected from the group consisting of

- a) building block polynucleotides comprising at least 1 reactant comprising at least 1 reactive group
- 5            b) building block polynucleotides comprising at least 1 reactive group,
- c) building block polynucleotides comprising at least 1 spacer region,
- 10           ii)     forming a hybridization complex comprising at least 4 building block polynucleotides,
- wherein at least 2 of said building block polynucleotides comprise at least 1 reactant comprising at least 1 reactive group,
- 15           wherein at least 1 of said building block polynucleotide hybridizes to at least 2 other building block polynucleotides, and
- iii)     synthesising the at least one molecule by reacting at least 2 reactants.
- 20        109.        The method of claim 108, comprising the steps of
- i)     providing m building block polynucleotides selected from the group consisting of
- 25           a) building block polynucleotides comprising at least 1 functional entity comprising at least 1 reactive group,
- b) building block polynucleotides comprising at least 1 reactive group,
- 30           c) building block polynucleotides comprising at least 1 spacer region and no functional entity or reactive group,
- wherein m is an integer of at least 4 and preferably less than 200,

- ii) hybridizing the m building block polynucleotides to form a hybridization complex,

5 wherein at least 2 of said building block polynucleotides comprise at least 1 functional entity comprising at least 1 reactive group,

wherein at least 1 of said building block polynucleotides hybridizes to at least 2 other building block polynucleotides,

10 with the proviso that no single building block polynucleotide hybridizes to the remaining m-1 building block polynucleotides,

- iii) reacting at least 3 functional entity reactive groups by reacting at least 1 reactive group of each functional entity,

15 wherein the reaction of said functional entity reactive groups results in the formation of the molecule by covalently linking at least 2 functional entities provided by separate building block polynucleotides.

20 110. The method of claim 109, wherein m is 4, and wherein the complex comprises

i) p building block polynucleotides comprising at least 1 functional entity comprising at least 1 reactive group,

25 ii) q building block polynucleotides comprising at least 1 reactive group, and

iii) r building block polynucleotides comprising at least 1 spacer region and no functional entity or reactive group,

30 wherein  $p + q + r$  is 4,

wherein p is an integer of from 2 to 4,

35 wherein q is an integer of from 0 to 2,

wherein the sum of p and q is 4 or less,

and

5 wherein the value of r is given by  $r = 4 - (p + q)$ .

111. The method of claim 107, wherein m is 6, and wherein the complex comprises

- 10 i) p building block polynucleotides comprising at least 1 functional entity comprising at least 1 reactive group,
- ii) q building block polynucleotides comprising at least 1 reactive group, and
- 15 iii) r building block polynucleotides comprising at least 1 spacer region and no functional entity or reactive group,

wherein  $p + q + r$  is 6,

20 wherein p is an integer of from 2 to 6,

wherein q is an integer of from 0 to 4, preferably an integer of from 0 to 2,

wherein the sum of p and q is 6 or less, and

25

wherein the value of r is given by  $r = 6 - (p + q)$ .

112. The method of claim 107, wherein m is 8, and wherein the complex comprises

30

- i) p building block polynucleotides comprising at least 1 functional entity comprising at least 1 reactive group,
- ii) q building block polynucleotides comprising at least 1 reactive group, and

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iii) r building block polynucleotides comprising at least 1 spacer region and no functional entity or reactive group,

wherein  $p + q + r$  is 8,

wherein p is an integer of from 3 to 8,

wherein q is an integer of from 0 to 5, preferably an integer of from 0 to 3,

wherein the sum of p and q is 8 or less, and

wherein the value of r is given by  $r = 8 - (p + q)$ .

113. The method of any of claims 109 to 112, wherein at least 3 of said building block polynucleotides comprise at least 1 functional entity comprising at least 1 reactive group,

wherein the number of building block polynucleotides hybridizing to at least 2 other building block polynucleotides is in the range of from 1 to m.

with the proviso that no single building block polynucleotide hybridises to the remaining m-1 building block polynucleotides.

114. The method of any of claims 109 to 112, wherein the sum of q and r is at least 1.

115. A method for synthesising a plurality of different molecules, said method comprising the steps of

i) providing a plurality of at least 1000 different building block polynucleotides each comprising at least one reactant, such as at least 5000 different building block polynucleotides each comprising at least one reactant, for example at least 10000 different building block polynucleotides each comprising at least one reactant, such as at least 20000 different building block polynucleotides each comprising at least one reactant, for example at least 30000 different building block polynucleotides

- each comprising at least one reactant, such as at least 40000 different building block polynucleotides each comprising at least one reactant, for example at least 50000 different building block polynucleotides each comprising at least one reactant, such as at least 60000 different building block polynucleotides each comprising at least one reactant, for example at least 70000 different building block polynucleotides each comprising at least one reactant, such as at least 80000 different building block polynucleotides each comprising at least one reactant, for example at least 100000 different building block polynucleotides each comprising at least one reactant,
- ii) selecting or providing from said plurality of building block polynucleotides  $n$  different building block polynucleotides for the synthesis of each different molecule, wherein  $n$  is an integer of at least 3 and preferably less than 200, such as 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 40, 50, 75, 100, or 150,
- iii) optionally further providing to the reaction compartment a plurality of building block polynucleotides selected from the group consisting of building block polynucleotides comprising at least 1 reactive group (type II) and building block polynucleotides comprising at least 1 spacer region and no functional entity or reactive group (type III),
- iv) hybridizing at least the selected or provided  $n$  building block polynucleotides to form a hybridization complex,
- wherein at least  $n$  of said building block polynucleotides comprise at least 1 reactant comprising at least 1 reactive group,
- wherein at least 1 of said building block polynucleotides hybridizes to at least 2 other building block polynucleotides,
- with the proviso that no single building block polynucleotide hybridizes to the remaining  $n-1$  building block polynucleotides, and
- v) reacting the at least  $n$  reactants by reacting at least 1 reactive group of each reactant, wherein the reaction of said reactants provided by separate building block



polynucleotides results in the formation of at least one molecule, wherein the at least one molecule is preferably linked to at least one building block polynucleotide by at least one linker, and

- 5 repeating the steps ii) to v) for different selections or provisions of building block polynucleotides each comprising at least one reactant, thereby generating a plurality of different molecules.

10 116. The method of claim 115 comprising the further steps of targeting the plurality of bifunctional molecules obtained from the method of claim 115 to at least one binding partner for at least one of said molecule parts of said bifunctional molecules, selecting at least one bifunctional molecule having an increased affinity for said binding partner, and identifying the molecule part of the bifunctional molecule by decoding the polynucleotide part of the plurality of building block polynucleotides forming  
15 the hybridisation complex of said bifunctional molecule.

117. The method of claim 116 comprising the further step of improving the binding of said molecule part to said binding partner, said improvement comprising the steps of isolating building block polynucleotides from the isolated bifunctional molecule, optionally separating building block polynucleotides into fractions depending on  
20 whether or not they have donated a reactant to the synthesis of the at least one molecule, hybridising some or all of said isolated building block polynucleotides with a plurality of building block polynucleotides each comprising at least one reactant, forming a plurality of second or further bifunctional molecules by reacting said reactants and linking said molecules to at least one building block polynucleotide of their  
25 respective hybridisation complexes, targeting said plurality of second or further bifunctional molecules to at least one target comprising a conceivable binding partner for the molecule parts of said plurality of bifunctional molecules, and selecting bifunctional molecules having improved binding affinities for said at least one target.

30